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Health Effects Assessment for Selected Phthalic Acid Esters

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ENVIRONMENTAL CRITERIA AND ASSESSMENT OFFICE
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16. ABSTRACT

This report summarizes and evaluates information relevant to a preliminary interim assessment of adverse health effects associated with specific chemicals or compounds. The Office of Emergency and Remedial Response (Superfund) uses these documents in preparing cost-benefit analyses under Executive Order 12991 for decision-making under CERCLA. All estimates of acceptable intakes and carcinogenic potency presented in this document should be considered as preliminary and reflect limited resources allocated to this project. The intent in these assessments is to suggest acceptable exposure levels whenever sufficient data are available. The interim values presented reflect the relative degree of hazard associated with exposure or risk to the chemical(s) addressed. Whenever possible, two categories of values have been estimated for systemic toxicants (toxicants for which cancer is not the endpoint of concern). The first, RfD_S or subchronic reference dose, is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs during a limited time interval. The RfD is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs for a significant portion of the lifespan. For compounds for which there is sufficient evidence of carcinogenicity, q_1^*s have been computed, if appropriate, based on oral and inhalation data if available.

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PREFACE

This report summarizes and evaluates information relevant to a preliminary interim assessment of adverse health effects associated with selected phthalic acid esters. All estimates of acceptable intakes and carcinogenic potency presented in this document should be considered as preliminary and reflect limited resources allocated to this project. Pertinent toxicologic and environmental data were located through on-line literature searches of the TOXLINE, CANCERLINE and the CHEMFATE/DATALOG data bases. The basic literature searched supporting this document is current up to May, 1986. Secondary sources of information have also been relied upon in the preparation of this report and represent large-scale health assessment efforts that entail extensive peer and Agency review. The following Office of Health and Environmental Assessment (OHEA) sources have been extensively utilized:

U.S. EPA. 1980a. Ambient Water Quality Criteria for Phthalate Esters. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Water Regulations and Standards, Washington, DC. EPA 440/5-80-067. NTIS PB81-117780.

U.S. EPA. 1980b. Hazard Profile for Phthalate Esters. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste, Washington, DC.

U.S. EPA. 1980c. Hazard Profile for Butyl Benzyl Phthalate. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste, Washington, DC.

U.S. EPA. 1980d. Hazard Profile for Di-n-butyl Phthalate. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste, Washington, DC.

U.S. EPA. 1980e. Hazard Profile for Diethyl Phthalate. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste, Washington, DC.

U.S. EPA. 1980f. Hazard Profile for Di-n-Octyl Phthalate. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste, Washington, DC.

U.S. EPA. 1980g. Hazard Profile for Bis(2-ethylhexyl) Phthalate. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste, Washington, DC.

U.S. EPA. 1983a. Reportable Quantity Document for 1,2-Benzenedicarboxylic acid, dibutyl ester (Dibutyl phthalate). Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Emergency and Remedial Response, Washington, DC.

U.S. EPA. 1983b. Reportable Quantity Document for 1,2-Benzenedicarboxylic acid, diethyl ester (Diethyl phthalate). Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Emergency and Remedial Response, Washington, DC.

U.S. EPA. 1985a. Drinking Water Criteria Document for Phthalic Acid Esters. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Drinking Water, Washington, DC. Draft.

The intent in these assessments is to suggest acceptable exposure levels for noncarcinogens and risk cancer potency estimates for carcinogens whenever sufficient data were available. Values were not derived or larger uncertainty factors were employed when the variable data were limited in scope tending to generate conservative (i.e., protective) estimates. Nevertheless, the interim values presented reflect the relative degree of hazard or risk associated with exposure to the chemical(s) addressed.

Whenever possible, two categories of values have been estimated for systemic toxicants (toxicants for which cancer is not the endpoint of concern). The first, RfD_S (formerly AIS) or subchronic reference dose, is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs during a limited time interval (i.e., for an interval that does not constitute a significant portion of the lifespan). This type of exposure estimate has not been extensively used, or rigorously defined, as previous risk assessment efforts have been primarily directed towards exposures from toxicants in ambient air or water where lifetime exposure is assumed. Animal data used for RfD_S estimates generally include exposures with durations of 30-90 days. Subchronic human data are rarely available. Reported exposures are usually from chronic occupational exposure situations or from reports of acute accidental exposure. These values are developed for both inhalation (RfD_{SI}) and oral (RfD_{SO}) exposures.

The RfD (formerly AIC) is similar in concept and addresses chronic exposure. It is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs for a significant portion of the lifespan [see U.S. EPA (1980b) for a discussion of this concept]. The RfD is route-specific and estimates acceptable exposure for either oral (RfD_O) or inhalation (RfD_I) with the implicit assumption that exposure by other routes is insignificant.

Composite scores (CSs) for noncarcinogens have also been calculated where data permitted. These values are used for identifying reportable quantities and the methodology for their development is explained in U.S. EPA (1984).

For compounds for which there is sufficient evidence of carcinogenicity RfD_S and RfD values are not derived. For a discussion of risk assessment methodology for carcinogens refer to U.S. EPA (1980c). Since cancer is a process that is not characterized by a threshold, <u>any</u> exposure contributes an increment of risk. For carcinogens, q_1^*s have been computed, if appropriate, based on oral and inhalation data if available.

ABSTRACT

In order to place the risk assessment evaluation in proper context, refer to the preface of this document. The preface outlines limitations applicable to all documents of this series as well as the appropriate interpretation and use of the quantitative estimates presented.

Carcinogenicity data sufficient for derivation of a q_1^* were located only for bis(2-ethylhexyl) phthalate, which was associated with increased incidence of liver tumors in rats and mice of both sexes fed diets containing the compound (NTP, 1982a). An interim q_1^* of 8.36×10^{-3} $(mg/kg/day)^{-1}$ for oral exposure was derived. This compound is classified as a B2 carcinogen.

RfD_{SO} and RfD_O values and CSs were calculated for several phthalate esters based on their oral toxicity. For diethyl phthalate an RfD_{SO} and RfD_O of 525 and 52.5 mg/day were based on a 16-week study in rats (Brown et al., 1978). A CS of 8 was based on reduced reproductive capacity in a 2-generation study using mice (Reel et al., 1984).

An RfD_{SO} of 88 mg/day and an RfD_O of 8.8 mg/day for di-n-butyl phthalate were based on a 52-week dietary study using rats (Smith, 1953; U.S. EPA, 1980a). A CS of 12.8 was based on developmental toxicity using mice (Shiota and Nishimura, 1982; Shiota et al., 1980).

A CS of 7 was calculated based on chronic nephritis in a 2-year study using rats (Lehman, 1955). Data were considered inadequate for RfD development.

Limited evidence of carcinogenicity in rats was obtained for butyl benzyl phthalate. Female rats fed the material in the diet experienced a statistically significant increased incidence of leukemia and lymphomas (NTP, 1982b). A similar response, however, was not observed in male rats and a dose-related decrease in similar cancers was noted in male mice in the same experiment. Data were considered inadequate for quantitative risk estimate, but adequate for assignment of a Group C weight-of-evidence classification, possible human carcinogen. The text of the document describes possible development of RfD_{SO} and RfD_O values for noncarcinogenic endpoints.

For di-n-octyl phthalate, data were inadequate for RfD development; a CS of 6 was based on mild liver effects in a 7- to 12-month dietary experiment using rats (Piekacz, 1971).

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LIST OF ABBREVIATIONS

BCF	Bioconcentration factor
bw	Body weight
CAS	Chemical Abstract Service
CS	Composite score
DMSO	Dimethyl sulfoxide
FEL	Frank-effect level
LOAEL	Lowest-observed-adverse-effect level
MED	Minimum effective dose
MTD	Maximum tolerated dose
NOAEL	No-observed-adverse-effect level
NOEL	No-observed-effect level
ppm	Parts per million
RfD	Reference dose
RfD_I	Inhalation reference dose
RfD_O	Oral reference dose
RfD_S	Subchronic reference dose
RfD_{SI}	Subchronic inhalation reference dose
RfD_{SO}	Subchronic oral reference dose
RQ	Reportable quantity
RV_d	Dose-rating value
RV_e	Effect-rating value
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase

1. ENVIRONMENTAL CHEMISTRY AND FATE

Selected physical and chemical properties and available half-life data for dimethyl, diethyl, di-n-butyl, di-n-octyl, bis-(2-ethylhexyl) and butyl benzyl phthalate are presented in Table 1-1. These chemicals can be classified as benzenedicarboxylic acid diesters (U.S. EPA, 1980b-g).

In air, gaseous phthalic acid esters are predicted to react with hydroxyl radicals. The actual atmospheric half-life because of adsorption onto airborne particulate matter may be longer than the estimated half-life given in Table 1-1. Removal of phthalate esters from the atmosphere by wet and dry deposition has been observed (Kawamura and Kaplan, 1983; Altas and Glam, 1981; Karasek et al., 1978; Weschler, 1984).

In water, the phthalate esters apparently biodegrade, volatilize, adsorb to sediments and bioconcentrate depending upon the size and complexity of the ester chains, environmental conditions and presence of fulvic acids (Callahan et al., 1979). Studies indicate that phthalic acid esters undergo rapid primary degradation and mineralization (half-lives range from days to weeks) by bacteria commonly found in the environment (Saeger and Tucker, 1973a,b; Gledhill et al., 1980). The rates of degradation have been shown to decrease with increasing size and complexity of the phthalate chain. Monitoring data and sediment-water partitioning coefficients indicate that adsorption to suspended solids and sediments is also likely to occur for all the phthalates (Sullivan et al., 1982; Mabey et al., 1981), although complexation with fulvic acid can cause solubilization (Khan, 1980; Ogner and Schnitzer, 1970; Matsuda and Schnitzer, 1971).

TABLE 1-1

Physical and Chemical Properties and Half-Lives for Selected Phthalates[a]

Property	Dimethyl Phthalate	Diethyl Phthalate	Di-n-butyl Phthalate	Di-n-octyl Phthalate	Bis(2-ethylhexyl) Phthalate	Butyl Benzyl Phthalate
CAS number	131-11-3	84-66-2	84-74-2	117-84-0	117-81-7	85-68-7
Molecular weight	194.19	222.23	278.35	390.57	390.57	312.37
Vapor pressure (at 25°C)	1.7×10^{-6} mm Hg	1.7×10^{-6} mm Hg	7.3×10^{-5} mm Hg	1.4×10^{-4} mm Hg[b]	6.5×10^{-6} mm Hg	8.3×10^{-6} mm Hg
Water solubility (at 25°C)	4.00×10^{6} ug/L	1.08×10^{6} ug/L	11.2 mg/L	3.0 mg/L[c]	0.34 mg/L	2.69 mg/L
Log octanol/ water partition coefficient	1.56	2.47	4.79	5.22[d]	4.66-5.45	4.91
Bioconcentration factor	57 bluegill, Lepomis macrochirus	15-16 mullet, Mugil cephalus	158[e] (calculated)	333[e] (calculated)	42-886 various species of fresh and saltwater fish	663 bluegill, Lepomis macrochirus
Half-lives in Air:	vapor phase: 23.80 hours (estimated)	vapor phase: 22.20 hours[f] (estimated)	vapor phase: 18.44 hours (estimated)	vapor phase: 13.81 hours[f] (estimated)	vapor phase: 11.86 hours (estimated)	vapor phase: 14.29 hours (estimated)
Water:	days to weeks (in unadsorbed state)	days to weeks (in unadsorbed state)	days to weeks (in unadsorbed state)	days to weeks (in unadsorbed state)	days to weeks (in unadsorbed state)	days to weeks (in unadsorbed state)
Soil:	4-5 days	days	3-4 days	days	10-20 days	days

[a]Source: Howard et al., 1985 (unless indicated otherwise)

[b]Mabey et al., 1981

[c]Wolfe et al., 1980

[d]Hansch and Leo, 1985

[e]Estimated using the equation: log BCF = 2.791-0.564 log S (Lyman et al., 1982)

[f]U.S. EPA, 1986a

Phthalic acid ester half-lives in soil were estimated from biodegradation data from a garden soil study (Shanker et al., 1985). Removal by mechanisms other than biodegradation, however, may also be significant from lower molecular weight phthalates. For example, dimethyl and diethyl phthalate are predicted to be highly mobile in soil and also have the potential to volatilize from dry soil surfaces. Overall, short-chain phthalates biodegrade at a faster rate than longer chain phthalates and anaerobic degradation is slower than aerobic degradation (Shanker et al., 1985).

2. ABSORPTION FACTORS IN HUMANS AND EXPERIMENTAL ANIMALS

2.1. ORAL

Absorption factors per se for the phthalate esters could not be located in the available literature. In general, excretion profiles indicate that alkyl phthalic acid esters and/or their degradation products are probably well absorbed from the gastrointestinal tract.

When bis(2-ethylhexyl) phthalate (10 or 2000 ppm) was administered to rats in the diet, >90% of the administered dose was excreted as metabolites in the urine; the remainder was excreted in the feces (Williams and Blanchfield, 1974). When bis(2-ethylhexyl) phthalate was administered to rats by gavage (3 or 1000 mg/kg, vehicle = corn oil), 42-54% of the administered dose was excreted as metabolites in the urine, while 24-57% was excreted as metabolites in the feces within 1-4 days (Williams and Blanchfield, 1974; Daniel and Bratt, 1974). When treated by gavage with 100 mg/kg ^{14}C-bis-(2-ethylhexyl) phthalate in corn oil, rats, mice and cynomologus monkeys excreted ~30-40% of the radioactive dose in the urine within 24 hours and ~50% of the radioactive dose in the feces within 24 hours (rats and mice) or 48 hours (monkeys) (A.D. Little, Inc., 1984). Blood levels of radioactivity were higher in monkeys than in rats or mice. In humans, 10-15% of a single oral dose of bis(2-ethylhexyl) phthalate was excreted in the urine as metabolites within 24 hours of administration (Schmid and Schlatter, 1985). Absorption of bis(2-ethylhexyl) phthalate and/or its degradation products may be greater than urinary levels of metabolites would indicate, since substantial biliary excretion has been observed in rats, dogs and miniature pigs (Daniel and Bratt, 1974; Ikeda et al., 1980).

Gastrointestinal absorption of di-n-butyl phthalate can be inferred from observations that >90% of a single dose of di-n-butyl phthalate administered

to rats by gavage (60, 270 or 2310 mg/kg, vehicles = corn oil, DMSO) was excreted as metabolites in the urine within 2 days; the remainder was excreted in the feces (Tanaka et al., 1978; Williams and Blanchfield, 1975).

Apparent hydrolytic activity toward bis(2-ethylhexyl) phthalate in pancreatic homogenates led Albro and Thomas (1973) to hypothesize that very little, if any, intact phthalate diester is absorbed from the gastrointestinal tract. Further studies have shown that phthalate esters [bis(2-ethylhexyl] phthalate, dimethyl phthalate, di-n-butyl phthalate, di-n-octyl phthalate) are readily hydrolyzed to their monoester derivatives by enzymes in intestinal mucosal cells (Rowland, 1974; White et al., 1980) and other tissues (Carter et al., 1974), and by extracellular enzymes present in the intestinal contents of rats, ferrets and baboons (Rowland, 1974; Rowland et al., 1977; Lake et al., 1977a).

Recent gavage studies on rats demonstrated that bis(2-ethylhexyl) phthalate was hydrolyzed to monoethylhexyl phthalate, which was subsequently absorbed (Teirlynck and Belpaire, 1985; Oishi and Hiraga, 1982). Teirlynck and Belpaire (1985) reported that plasma concentrations of 8.8±1.7 µg/mL bis(2-ethylhexyl) phthalate and 63.2±8.7 µg/mL monoethylhexyl phthalate were reached within 3 hours after a single oral dose of bis(2-ethylhexyl) phthalate (2.8 g/kg in corn oil). Pollack et al. (1985) found that 80% of a single oral (gavage in corn oil) dose of bis(2-ethylhexyl) phthalate was hydrolyzed to its monoester derivative (monoethylhexyl phthalate) and subsequently absorbed; 13% of the dose was absorbed as bis(2-ethylhexyl) phthalate. The ratio of the area under the curves for monoethylhexyl phthalate to di(2-ethylhexyl) phthalate was ~7. Repetitive oral dosing did not affect the extent of absorption.

2.2. INHALATION

Pertinent quantitative data regarding the absorption of phthalate esters by inhalation could not be located in the available literature. Pegg (1982) exposed adult male Sprague-Dawley rats to ^{14}C-bis(2-ethylhexyl) phthalate aerosol at 100 mg/m^3 for 6 hours in a heads-only exposure chamber. Radioactivity equivalent to 3.83 µmol of parent compound was recovered from urine, feces, skin and carcass, 72 hours after exposure. In another phase of the experiment, radioactivity equivalent to 3.94 µmol of parent compound was recovered from urine, feces, skin and carcass 72 hours after oral administration of 25 µmol/kg parent compound. On the basis of these results and the blood levels of radioactivity measured at several intervals following exposure, the investigators concluded that absorption is rapid and extensive, following inhalation exposure. Noting the clearance of radioactivity from lung tissue following exposure, the investigators concluded that absorption from the lung is rapid and virtually complete.

3. TOXICITY IN HUMANS AND EXPERIMENTAL ANIMALS

Chronic or subchronic oral studies have been conducted with bis(2-ethylhexyl), di-n-butyl, diethyl, butyl benzyl and di-n-octyl phthalates. The liver, kidney and testes appear to be the organs affected most by phthalic acid esters. Only those studies having a direct bearing on risk assessment are reported in this document.

3.1. SUBCHRONIC

3.1.1. Oral.

3.1.1.1. BIS(2-ETHYLHEXYL) PHTHALATE -- Subchronic oral studies have been conducted with bis(2-ethylhexyl) phthalate on rats (Shaffer et al., 1945; Harris et al., 1955; Nikonorow et al., 1973; Gray et al., 1977; Gangolli, 1982; Popp et al., 1985; Nagasaki et al., 1974; Maslenko, 1968), mice (Nagasaki et al., 1974; Ota et al., 1974), ferrets (Lake et al., 1976, 1977b), guinea pigs (Carpenter et al., 1953) and dogs (Carpenter et al., 1953; Harris et al., 1955). The studies in which adverse effects were observed at the lowest levels of exposure are those of Gray et al. (1977) and Nagasaki et al. (1974) using rats.

Gray et al. (1977) fed 0, 0.2, 1.0 or 2.0% bis(2-ethylhexyl) phthalate in the diet to groups of 15 male and 15 female Sprague-Dawley derived CD rats for 17 weeks. Dietary concentrations were equivalent to 0, 150, 750 and 1500 mg/kg/day (Gangolli, 1982). Body weight, food consumption, clinical signs of toxicity, serum biochemistry, urinalysis and hematology were monitored (Gray et al., 1977). Gross and microscopic pathological examinations were performed on all rats at the end of the study. Effects were observed at all levels of exposure. Significantly increased absolute and relative liver weights were observed in all exposed groups. Food consump-

tion and growth were reduced in rats fed 1 or 2% bis(2-ethylhexyl) phthalate. Compared with controls, significantly reduced testicular weights, significantly increased testicular damage (dose-related) and a significant decrease in hemoglobin concentration were observed in male rats fed the 1 or 2% concentration. Both males and females fed either 1 or 2% bis(2-ethylhexyl) phthalate had a significantly reduced packed cell volume compared with controls.

Nagasaki et al. (1974) reported that interstitial nephritis, increased SGPT and decreased blood glucose were observed in rats fed either 500 or 1000 ppm bis(2-ethylhexyl) phthalate in the diet for 48 weeks. The dietary levels were equivalent to 25 or 50 mg/kg/day, respectively, assuming that a rat consumes a daily amount of food equal to 5% of its body weight (U.S. EPA, 1980h). No other details were available.

3.1.1.2. DIETHYL PHTHALATE -- In a Food Research Labs. (1955) study, diethyl phthalate was fed to dogs at concentrations of 0.5% (three dogs), 1.5% (one dog), 2.0% (one dog) and 2.5% (three dogs) for 1 year. Food consumption varied throughout the study; average doses as reported by the investigator were 114, 343, 500 and 629 mg/kg/day. No effects were observed at any level of exposure, but the endpoints monitored were not reported.

Brown et al. (1978) fed groups of 15 male and 15 female CD rats 0, 0.2, 1.0 or 5.0% diethyl phthalate (0, 150, 770 or 3160 mg/kg/day, males; 0, 150, 750 or 3710 mg/kg/day, females) in the diet for 16 weeks. Variables monitored in the study included body weight, food consumption, water intake, hematology, urinalysis, serum biochemistries, and gross and microscopic pathology. Terminal body weights of male and female rats fed 5% diethyl phthalate and female rats fed 1% diethyl phthalate were reduced significantly compared with controls. Paired feeding studies indicated that these

reductions were not due to decreased food consumption. Compared with controls, statistically significant decreases in absolute organ weights (brain, heart, spleen, kidneys) and increases in relative organ weights (brain, liver, stomach, small intestine, full calcium, testes, kidneys) were observed in males and females fed 5.0% diethyl phthalate for 16 weeks. These changes were attributed to the compound-related effect on growth rate since dose-related changes in gross or microscopic pathology were not observed. No other effects were observed.

3.1.1.3. DI-n-BUTYL PHTHALATE -- The subchronic oral toxicity of di-n-butyl phthalate has been tested in rats (Smith, 1953; Nikonorow et al., 1973; Piekacz, 1971; Bornmann et al., 1956; Maslenko, 1968) and mice (Ota et al., 1974), but the only studies that reported effects were Smith (1953), Nikonorow et al. (1973) and Ota et al. (1974).

Smith (1953) fed 0, 0.01, 0.05, 0.25 or 1.25% di-n-butyl phthalate in the diet to groups of 10 male Sprague-Dawley rats for 1 year. Equivalent doses using a food factor of 5% are 0, 5, 25, 125 or 625 mg/kg/day. The only effect observed was 50% mortality during the first week of the study in the high-dose group.

Increased relative liver weight in the absence of histopathological liver lesions was observed in rats treated with 120 or 1200 mg/kg/day for 3 months (Nikonorow et al., 1973). Degenerative changes in the kidneys and liver occurred in mice fed 500 or 5000 mg di-n-butyl phthalate/kg bw/day in the diet for 1-3 months (Ota et al., 1974). No other details were given.

3.1.1.4. DIMETHYL PHTHALATE -- Pertinent data regarding the subchronic oral toxicity of dimethyl phthalate could not be located in the available literature.

3.1.1.5. BUTYL BENZYL PHTHALATE -- There are very few oral long-term BBP studies. In a draft report, NTP (1985) conducted a toxicity and mating trial study in F344 rats concomitantly. The toxicity portion of this report was conducted to determine the no toxic effect level and to evaluate the dose response of BBP. Rats were administered concentrations of either 0, 0.03, 0.09, 0.28, 0.83 or 2.50% BBP in the diet for 26 weeks. There were 15 male animals in each dose group, starting at 6 weeks of age. Throughout the study, body weight gain was significantly depressed at the 2.5% BBP level when compared with the controls. There were no deaths attributed to BBP toxicity. All the rats given 2.5% BBP had small testes upon gross necropsy at the 26-week termination. Five of 11 had soft testes and only 1/11 had a small prostate and seminal vesicle. In the 0.03, 0.09, 0.28 and 0.83% BBP dose groups there were no grossly observable effects on male reproductive organs. The kidneys of six animals in the 2.5% group contained focal cortical areas of infarct-like atrophy. In addition, testicular lesions were also observed at the 2.5% dose level. Lesions were characterized by atrophy of seminiferous tubules and aspermia. The other treatment groups showed no evidence of abnormal morphology in any other organs.

Histopathological changes were also seen at the 2.5% BBP level after 10 weeks of exposure in the mating trial portion of this study. After histopathological examination, testicular lesions were characterized by atrophy of seminiferous tubules and a near total absence of mature sperm production. When 10/30 females successfully mated with the 2.5% treatment level males, none were pregnant at necropsy. The investigators concluded that the data suggest a depression in male reproductive organ weights by either a direct or indirect toxic effect after 2.5% BBP administration. BBP at 0.83% in the diet did not result in any treatment-related effects as evaluated by the

authors. The investigators concluded from the results of both studies that a threshold for toxicity would be between 0.83 and 2.5% BBP.

In contrast to the author's conclusions, some alterations in animals fed 0.83% BBP were noted which may have been compound related in that they occurred in the 2.5% group also, but not in lower exposure groups. Liver-to-body weight ratios were significantly increased in both the 0.83 and 2.5% diet groups, while liver-to-brain weight ratio was increased in the 0.83% group alone. Absolute liver weight was also increased in the 0.83% group. Hematological evaluations showed small but significant elevations in mean corpuscular hemoglobin in the 0.83% group at 60, 90, 120 and 150 days, but not at 30 or 180 days, while mean corpuscular hemoglobin concentration was increased at 60 and 120 days. Interestingly, no alterations in these parameters was seen in the lower dose groups. The 2.5% group showed a consistent pattern of increased reticulocytes, decreased red blood cells, increased mean corpuscular volume, increased mean corpuscular hemoglobin and hemoglobin concentration in addition to reduced cellularity of the bone marrow.

Krauskopf (1973) reported 90-day feeding studies on rats and dogs (strains, sex, numbers not reported) conducted by Monsanto (1972). Rats were fed diets containing 0, 0.25, 0.5, 1.0, 1.5 or 2% (0, 125, 250, 500, 750 or 1000 mg/kg/day, assuming a food factor of 0.05) butyl benzyl phthalate, while dogs were fed diets containing 0, 1, 2 or 5% (0, 250, 500 or 1250 mg/kg/day, assuming a food factor of 0.025). No adverse effects were observed among dogs fed butyl benzyl phthalate at any level, or among rats fed 0.25 or 0.5% butyl benzyl phthalate. Increased liver weights without accompanying histopathological changes were observed among rats fed 1-2% butyl benzyl phthalate. Slightly reduced growth rate was observed at the two highest doses.

3.1.1.6. DI-n-OCTYL PHTHALATE -- An abstract of a Polish study (Piekacz, 1971) reported that groups of 40 male and female rats (strain not reported) were fed diets containing 0 or 3500 ppm (0 or 175 mg/kg/day, using a food factor of 0.05) di-n-octyl phthalate for 7-12 months. Elevated relative liver weight was observed among di-n-octyl phthalate-treated females at 7 and 12 months. SGOT and SGPT were significantly increased in both males and females at 12 months. Increased kidney weight was reported among females at 12 months. Effects on spleen weight or body weight were not observed. Histopathological examination was apparently not performed.

3.1.2. Inhalation. Pertinent data regarding the subchronic toxicity of inhalation of phthalate esters could not be located in the available literature.

3.2. CHRONIC

3.2.1. Oral.

3.2.1.1. BIS(2-ETHYLHEXYL) PHTHALATE -- Chronic oral toxicity studies with bis(2-ethylhexyl) phthalate have been conducted on rats (Carpenter et al., 1953; NTP, 1982a; Kluwe et al., 1982a; Ganning et al., 1985) and mice (NTP, 1982a; Kluwe et al., 1982a).

The study in which adverse effects were observed at the lowest levels of exposure is that of Carpenter et al. (1953). Groups of Sherman rats (32/sex/group) were fed 0, 0.04, 0.13 or 0.4% bis(2-ethylhexyl) phthalate in the diet (equivalent doses of 0, 20, 60 or 200 mg/kg/day provided by the investigators) for 2 years, and were allowed to breed within the first year. After 1 year, groups of eight males and eight females were continued on test for 1 more year. Groups of 32 male and 32 female progeny were chosen from the control and high-dose groups and placed on the appropriate control or high-dose diet for 1 year. Parental male rats and F_1 males and females

fed 0.4% bis(2-ethylhexyl)phthalate (200 mg/kg/day) had significantly increased liver and kidney weights, but no histopathological changes. No other compound-related effects were observed.

3.2.1.2. DIETHYL PHTHALATE -- U.S. EPA (1980a) summarized a study by Food Research Labs. (1955) in which groups of 30 rats (strain and sex not reported) were fed diets containing diethyl phthalate at concentrations of 0.5, 2.5 or 5.0% for 104 weeks. The dietary levels are equivalent to 250, 1250 or 2500 mg/kg/day, assuming a daily food consumption equal to 5% of the body weight (U.S. EPA, 1980h). The only effect observed was a small but significant reduction in growth rate among rats fed 5% diethyl phthalate. Food consumption was not affected. U.S. EPA (1980a) did not report endpoints monitored in the study.

3.2.1.3. DI-n-BUTYL PHTHALATE -- In chronic oral toxicity studies of di-n-butyl phthalate, unspecified numbers of rats were fed dietary concentrations of 0, 100 or 300 ppm for 21 months (Lefaux, 1968). No effects were observed.

3.2.1.4. DIMETHYL PHTHALATE -- Lehman (1955) fed groups of rats (number, sex and strain not reported) dimethyl phthalate at levels of 2, 4 or 8% in the diet (1000, 2000 or 4000 mg/kg/day using a food factor of 0.05) for 2 years. U.S. EPA (1980a) incorrectly attributed this study to Draize et al. (1948). No effects were observed among rats fed 2% dimethyl phthalate. A minor effect on growth was observed at 8%, while "nephritic involvement" at 8% was observed (U.S. EPA, 1980a).

3.2.1.5. BUTYL BENZYL PHTHALATE -- NTP (1982b) fed butyl benzyl phthalate in the diet to female F344 rats at concentrations of 0, 6000 or 12,000 ppm and to B6C3F1 mice of both sexes at concentrations of 0, 3000 or 6000 ppm for 103 weeks. The only noncarcinogenic effects observed in female

rats and male and female mice were reductions in growth rate in all treated groups. Growth rate reduction in female rats was accompanied by reduced food consumption. Food consumption data were not reported for mice. Male F344 rats were also fed 0, 6000 or 12,000 ppm n-butyl benzyl phthalate, but the study was terminated after 28 weeks because of high mortality among treated rats. Mortality was attributed to unexplained hemorrhaging.

3.2.1.6. DI-n-OCTYL PHTHALATE -- Pertinent data regarding chronic oral toxicity of di-n-octyl phthalate could not be located in the available literature.

3.2.2. Inhalation. The health status of 147 workers who handled phthalate plasticizers was evaluated by Milkov et al. (1973). Workers were exposed to a mixture of compounds including di-n-butyl phthalate, DAP-789, di-n-octyl phthalate, diisooctyl phthalate, butyl benzyl phthalate, selacinates, adipinates, vinyl chloride, carbon monoxide and mixed ethers. Phthalate exposure was estimated to be 1-40 mg/m^3. Effects attributed to phthalate exposure included polyneuritis (frequency and intensity increased with duration of employment), decline in vestibular and olfactory excitability and reductions in thrombocytes, leukocytes, hemoglobin and "blood color index."

Gilioli et al. (1978) performed clinical neurological electromyographic and electroneurologic tests on 38 workers in the phthalate plasticizer industry. Of the 38 workers, 23 had been exposed only to phthalate esters (not otherwise specified) for an average of 4.5 years; the remainder had been exposed only to alcohols or only to phthalic anhydride. Ambient concentrations of phthalate esters were <1-5 mg/m^3 in some areas and 5-60 mg/m^3 in others. Of the 23 workers exposed only to phthalate esters, 12 were found to have mild to moderate sensory-motor and motor polyneuropathy.

The frequency and severity increased with length of exposure; no cases were found in workers exposed for <2 years.

Thiess et al. (1978) examined morbidity among 101 workers employed in the production of bis(2-ethylhexyl) phthalate for an average of 12 years (range=4 months to 35 years). Exposure ranged from 0.0006-0.01 ppm (0.01-0.16 mg/m³). There was no evidence of a higher incidence of miscarriages or deformities of offspring among female workers or the wives of male workers. No other compound-related effects were observed, though bis(2-ethylhexyl) phthalate was found in the blood and urine of both exposed and control groups.

Chronic inhalation studies on phthalate esters in experimental animals could not be located in the available literature.

3.3. TERATOGENICITY AND OTHER REPRODUCTIVE EFFECTS

3.3.1. Oral. A number of oral studies have shown that exposure to bis(2-ethylhexyl) or di-n-butyl phthalate during gestation can have adverse effects upon the developing fetus. Whether the observed effects (reduced fetal weight, fetal mortality, gross external and skeletal malformations) represent a primary effect of the compound in question or whether they occur as a result of maternal toxicity has not been determined.

Bis(2-ethylhexyl) phthalate-induced fetotoxic and teratogenic effects have been reported in rats and mice (Wolkowski-Tyl, 1984a,b; Bell et al., 1979; Bell, 1980; Shiota and Mima, 1985; Shiota and Nishimura, 1982; Shiota et al., 1980; Nakamura et al., 1979; Yagi et al., 1978, 1980; Tomita et al., 1982; Onda et al., 1974; Nikonorow et al., 1973). Studies conducted by NTP (Wolkowski-Tyl et al., 1984a,b) indicate that mice are more sensitive to bis(2-ethylhexyl) phthalate than rats. The studies that show effects at the lowest level of exposure and in the absence of maternal toxicity report a

significantly increased incidence of malformed fetuses/litter in CD-1 mice whose dams were fed 91 mg/kg/day throughout gestation (Wolkowski-Tyl et al., 1984b); significantly decreased fetal body weight in ddY-SlcXCBA mice whose dams were gavaged with 0.05 mL/kg (49 mg/kg) on day 7 of gestation (Tomita et al., 1982); and the formation of renal cysts in the F_1 and F_2 generations of mice exposed orally (not otherwise specified) to 10 or 100 mg/kg/day for 3 generations (Onda et al., 1974) (no other details were provided). The decreased fetal body weights observed by Tomita et al. (1982) were not observed in ICR or CD-1 mice treated at somewhat higher (0.05% diet or ~65 mg/kg/day) or lower (44 mg/kg/day) doses throughout gestation (Wolkowski-Tyl et al., 1984b; Shiota et al., 1980; Shiota and Nishimura, 1982). The study conducted by Wolkowski-Tyl et al. (1984b) provided a NOEL of 44 mg/kg/day and a LOAEL of 91 mg/kg/day for bis(2- thylhexyl) phthalate-promoted teratogenic effects.

Plasterer et al. (1985) reported that dimethyl phthalate had no effects on reproduction in CD-1 mice. Groups of 50 female mice were gavaged with 0 or the MTD (3500 mg/kg/day) of dimethyl phthalate in corn oil on days 7-15 of gestation, and allowed to deliver naturally. There were no significant effects on survival, body weight, birth weight of pups, average number live/litter, average number dead/litter, or average weight of pups on days 1 and 3 postpartum. The pups were not examined for malformations.

Shiota et al. (1980) and Shiota and Nishimura (1982) reported teratogenic effects and resorptions in mice caused by di-n-butyl phthalate, but only at a dietary concentration (1%) that also produced a significant depression of maternal weight gain. Dietary levels tested were 0, 0.05, 0.1, 0.2, 0.4 and 1.0%, corresponding to intakes of 0, 80, 180, 370, 660 and 2100 mg/kg/day. No serious effects on the fetuses or dams were observed in

mice fed ≤0.4% di-n-butyl phthalate throughout gestation. Coccygeal ossification was retarded in all treated groups. In a 3-generation study, Onda et al. (1974) observed renal cyst formation in the F_1 and F_2 generations of mice exposed orally (not otherwise specified) to 10 or 100 mg di-n-butyl phthalate/kg/day, but no other details were given. An increased number of resorptions and significantly reduced fetal body weights were observed in rats gavaged with 600 mg di-n-butyl phthalate/kg/day throughout gestation (Nikonorow et al., 1973); reduced placental weights were observed in mice gavaged with 120 or 600 mg di-n-butyl phthalate/kg/day. This study, however, did not randomly select test animals and the animals were not examined for gross or visceral malformations.

A recent study indicated that phthalic acid esters may cause adverse effects when transported to the developing organism by milk. Parmar et al. (1985) observed a decrease in weight gain and changes in enzyme levels indicative of liver damage in 21-day-old rat pups whose dams were gavaged with 2000 mg bis(2-ethylhexyl) phthalate/kg throughout lactation.

NTP recently conducted reproduction and fertility assessments on CD-1 mice for diethyl phthalate (Reel et al., 1984) and di-n-octyl phthalate (Gulati et al., 1985) by using the "fertility assessment by continuous breeding" protocol, which consists of four tasks: 1) a range-finding study to determine MTD; 2) a continuous breeding study entailing exposure during 7 days before mating, 98 days of cohabitation and 21 days of segregation; 3) a cross-over breeding study to determine the affected sex; and 4) a reproductive performance assessment of control and high-dose litters from Task 2. Task 3 is performed only if adverse effects are detected in Task 2. If no adverse effects are detected in Task 2, then Task 4 is performed.

Based on the range-finding studies, dietary concentrations of 0, 0.25, 1.25 and 2.5% diethyl phthalate and 0, 1.25, 2.5 and 5% di-n-octyl phthalate were chosen for Task 2. No adverse compound-related effects (number of pairs able to produce at least one litter, number of litters/pair, proportion of pups born alive, sex of pups born alive, live pup weight) were observed for either diethyl phthalate or di-n-octyl phthalate; therefore, Task 4 was performed for both compounds. Endpoints monitored for Task 4 included body weight at weaning and at 74 days of age, mating behavior, reproductive performance as measured in Task 2 (beginning at 74 days of age), sperm assessment and selected organ weights. F_1 male and female pups born to dams fed 2.5% diethyl phthalate had significantly lower body weights than controls at weaning and at 74 days of age. The diethyl phthalate-exposed F_1 mice had significantly fewer live pups per litter than did controls. Males had significantly reduced sperm concentrations and significantly increased prostate weights in comparison with controls. Both males and females exposed to diethyl phthalate had significantly increased liver weights; females also had significantly increased pituitary weights. In contrast, there were no significant, adverse compound-related effects on fertility, reproduction or organ weights in F_1 mice exposed to 5% di-n-octyl phthalate.

The fertility of Sherman rats was not affected by dietary exposure to bis(2-ethylhexyl) phthalate (up to 0.4%). Significantly increased relative kidney and liver weights, however, were observed in F_1 males and females (Carpenter et al., 1953).

The testicular effects of phthalic acid esters have been studied extensively in rats. Orally administered bis(2-ethylhexyl) phthalate, di-n-butyl phthalate and butyl benzyl phthalate cause testicular atrophy characterized

in general by reduced testicular weight, histological evidence of degeneration, reduced testicular zinc concentration and either an increase or decrease in testicular testosterone concentration (Gray et al., 1977, 1982; Gangolli, 1982; Oishi and Hiraga, 1980, 1983; Gray and Butterworth, 1980; Mangham et al., 1981; Oishi, 1985; Agarwal et al., 1985; Cater et al., 1976, 1977; NTP, 1982a; Kluwe et al., 1982a). Cater et al. (1977) demonstrated that co-administration of zinc could counteract the degenerative effects of di-n-butyl phthalate, while Oishi and Hiraga (1983) demonstrated that co-administration of zinc had no effect on bis(2-ethylhexyl) phthalate-promoted atrophy. Furthermore, Gray and Butterworth (1980) demonstrated that when exposure to bis(2-ethylhexyl) phthalate was discontinued in rats, testicular weight and morphology were restored within 12-20 weeks; Oishi (1985) observed only slight recovery after 45 days. Equimolar concentrations of dimethyl phthalate, diethyl phthalate and di-n-octyl phthalate did not cause testicular atrophy in rats when administered orally for 4-10 days (Gray and Butterworth, 1980; Foster et al., 1980).

Species differences in phthalic acid ester-promoted testicular atrophy have also been observed. Gray et al. (1982) failed to observe testicular atrophy in hamsters gavaged with di-n-butyl and bis(2-ethylhexyl) phthalates at equimolar doses equivalent to those that caused atrophy in rats. In the same study, mice gavaged with equimolar doses of di-n-butyl and bis(2-ethylhexyl) phthalates had only slight focal atrophy. B6C3F1 mice fed 6000 ppm (1325 mg/kg/day) bis(2-ethylhexyl) phthalate in the diet for 103 weeks had a slight but significantly higher incidence of seminiferous tubule atrophy than controls (NTP, 1982a; Kluwe et al., 1982a).

3.3.2. Inhalation. Data pertaining to the teratogenic or reproductive effects in laboratory animals of inhaled phthalates could not be located in the available literature.

Aldyreva et al. (1974) reported an increase in the incidence of miscarriages and menstrual disorders among women exposed to phthalate esters in the synthetic leather industry. Details concerning the exposed and control populations were not given.

4. CARCINOGENICITY

4.1. HUMAN DATA

Data regarding the carcinogenicity of phthalate esters in humans could not be located in the available literature.

4.2. BIOASSAYS

4.2.1. Oral. Bis(2-ethylhexyl) and butyl benzyl phthalates have been tested for oncogenicity in NTP-directed feeding studies on rats and mice (NTP, 1982a,b). Wilbourn and Montesano (1982) reviewed other oral studies on bis(2-ethylhexyl) phthalate (Carpenter et al., 1953; Harris et al., 1955) conducted before the NTP bioassays and concluded that they were insufficient to assess the carcinogenic potential of phthalate esters because of design and reporting limitations; U.S. EPA (1985) concurred with this evaluation. The NTP (1982a,b) studies, though not flawless, provided the only reasonable tests of oncogenicity.

Butyl benzyl phthalate at 0, 6000 or 12,000 ppm in the diet was fed to groups of 50 male and 50 female F344/N rats and 50 male and 50 female B6C3F1 mice for 28 weeks (male rats only) or 103 weeks (mice and female rats) (NTP, 1982b). Control mice and female control rats were killed after 106 weeks of testing; treated male rats and male controls were killed after 29 weeks; and male and female mice and female rats exposed to butyl benzyl phthalate were killed after 104-106 weeks. Endpoints monitored included body weight, food consumption, mortality, clinical signs of toxicity, and gross and microscopic pathology. When treated animals were compared with controls, a number of compound-related effects were observed. Increased mortality associated with "unexplained internal hemorrhaging" was observed in butyl benzyl phthalate-exposed male rats beginning at the 14th week of exposure. Consequently, the study on male rats was terminated after week 28 of exposure.

Survival curves were comparable for treated and control mice and female rats. Reduced body weights were observed in all rats and mice fed n-butyl benzyl phthalate. The reduction was slight in female rats but substantial in male and female mice. Food consumption was reduced 70-80% in treated female rats, but food consumption data were not reported for mice and male rats. A statistically significant increase ($p=0.011$, Fisher Exact test) in mononuclear cell leukemia was observed in high-dose female rats (Table 4-1) and was frequently accompanied by splenomegaly and hepatomegaly. A statistically significant increase in leukemia or lymphoma was also observed in high-dose female rats ($p=0.007$, Fisher Exact test). No other compound-related increases in neoplastic or nonneoplastic lesions were observed in female rats. The study on male rats was too brief to provide meaningful analysis of the data. No compound-related increases in the incidences of neoplastic or nonneoplastic lesions were observed in mice of either sex. Dose-related and significant decreases in mammary gland adenomas (female rats), alveolar/bronchiolar adenomas or carcinomas (male mice), lymphomas (male mice), and lymphomas or leukemia (male mice) were observed (see Table 4-1).

NTP (1982b) concluded that butyl benzyl phthalate was "probably carcinogenic for female F344/N rats." In a separate report, Kluwe et al. (1982b), however, concluded that since the background incidence of myelomonocytic leukemia is normally high in F344/N rats (8-15% and 9-24% in females and males, respectively), results presented in NTP (1982b) provide only equivocal evidence of butyl benzyl phthalate-induced cancer in female rats. Furthermore, the fact that significant and dose-related decreases in incidences of malignant lymphoma, all lymphoma, and lymphoma or leukemia were observed in male mice contributes to the uncertainty that butyl benzyl phthalate may cause leukemia in humans. IARC (1982a) concluded that the NTP

TABLE 4-1

Hematopoietic Neoplasms in F344/N Rats and B6C3F1 Mice Fed Butyl Benzyl Phthalate in the Diet for 103 Weeks[a]

Species	Sex	Tumor Type	Incidence (p value)[b]		
			Control	Low Dose (6000 ppm)	High Dose (12,000 ppm)
Rat	F	mononuclear cell leukemia	7/49 (0.006)	7/49 (NS)	18/50 (0.011)
		leukemia or lymphoma	7/49 (0.004)	7/49 (NS)	19/50 (0.007)
Mouse	M	malignant lymphoma	12/50 (0.024N)[c]	10/49 (NS)	4/50 (0.027N)[c]
		all lymphomas	13/50 (0.015N)[c]	11/49 (NS)	4/50 (0.016N)[c]
		lymphoma or leukemia	14/50 (0.008N)[c]	11/49 (NS)	4/50 (0.009N)[c]
	F	malignant lymphoma	15/50 (NS)	14/50 (NS)	15/50 (NS)
		all lymphomas	17/50 (NS)	16/50 (NS)	17/50 (NS)
		lymphoma or leukemia	17/50 (NS)	16/50 (NS)	18/50 (NS)

[a]Source: NTP, 1982b

[b]The p-values next to the control incidences indicate the probability level for the Cochran-Armitage test; p-values next to dosed-group incidences indicate the probability level for the Fisher Exact test.

[c]N indicates a negative trend; that is, the incidence for dosed groups is lower than for controls.

NS = Not significant ($p>0.05$)

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(1982b) studies were insufficient to assess the carcinogenic potential of butyl benzyl phthalate.

Bis(2-ethylhexyl) phthalate was fed to groups of 50 male and 50 female F344 rats at levels of 0, 6000 or 12,000 ppm, and to groups of 50 male and 50 female B6C3F1 mice at levels of 0, 3000 or 6000 ppm in the diet for 103 weeks (NTP, 1982a; Kluwe et al., 1982a). Average doses calculated from data on food consumption and body weight were 322 and 674 mg/kg/day for low- and high-dose male rats, 394 and 774 mg/kg/day for low- and high-dose female rats, 672 and 1325 mg/kg/day for low- and high-dose male mice, and 799 and 1821 mg/kg/day for low- and high-dose female mice, respectively. Throughout the study, food consumption, body weight, mortality and clinical signs of toxicity were monitored. Animals surviving 103 weeks on the test were maintained for an additional 1-2 weeks after treatment, then evaluated by necropsy and histopathology. Animals that died before 103 weeks were evaluated similarly.

There were no compound-related effects on survival. A number of compound-related effects were observed when treated animals were compared with controls. A moderate decrease in body weight was observed in bis(2-ethylhexyl) phthalate-treated female mice, but was not accompanied by a reduction in food consumption. Body weight was reduced moderately in low- and high-dose male rats and high-dose female rats, but food consumption was also slightly reduced. A significantly higher incidence (Fisher Exact test) of hepatocellular carcinoma was observed in high-dose female rats, middle- and high-dose female mice and high-dose male mice (Table 4-2). A significantly greater incidence (Fisher Exact test) of hepatocellular carcinoma or neoplastic nodules was observed in high-dose male rats, middle- and high-

TABLE 4-2

Liver Neoplasms in F344/N Rats and B6C3F1 Mice Fed Bis(2-ethylhexyl) Phthalate in the Diet for 103 Weeks[a]

Species	Sex	Tumor Type	Incidence (p value)[b]		
			Control	Low Dose[c]	High Dose[c]
Rat	M	hepatocellular carcinoma	1/50 (0.047)	1/49 (NS)	5/49 (NS)
		hepatocellular carcinoma or neoplastic nodule	3/50 (0.007)	6/49 (NS)	12/49 (0.01)
	F	hepatocellular carcinoma	0/50 (0.002)	2/49 (NS)	8/50 (0.003)
		hepatocellular carcinoma or neoplastic nodule	0/50 (<0.001)	6/49 (0.012)	13/50 (<0.001)
Mouse	M	hepatocellular carcinoma	9/50 (0.018)	14/48 (NS)	19/50 (0.022)
		hepatocellular carcinoma or adenoma	14/50 (0.002)	25/48 (0.013)	29/50 (0.002)
	F	hepatocellular carcinoma	0/50 (<0.001)	7/50 (0.006)	17/50 (<0.001)
		hepatocellular carcinoma or adenoma	1/50 (<0.001)	12/50 (0.001)	18/50 (<0.001)

[a]Source: NTP, 1982a

[b]The p value next to the control incidence indicates the probability level for the Cochran-Armitage test; the p value next to the dosed group incidence indicates the probability level for the Fisher Exact test.

[c]Rats were given dietary concentrations of 6000 and 12,000 ppm; mice were given 3000 and 6000 ppm.

NS = Not significant (p>0.05)

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dose female rats and a significantly greater incidence of hepatocellular carcinoma or adenoma was observed in middle- and high-dose male and female mice (see Table 4-2). Significantly decreased incidences of interstitial cell tumors of the testes, pituitary carcinoma or adenoma and thyroid C-cell carcinoma or adenoma were also observed in high-dose male rats.

NTP (1982a), Kluwe et al. (1982a), U.S. EPA (1985) and IARC (1982b) concluded that these results provide sufficient evidence of bis(2-ethylhexyl) phthalate-induced carcinogenicity in rats and mice. This conclusion, however, is disputed. Northrup et al. (1982) claim that the NTP (1982a) results are equivocal since the MTD was exceeded in some treatment groups, incidences of liver tumors varied within different control groups of the same species and sex, and treated animals may have been malnourished. Northrup et al. (1982) also claimed that the rodent data cannot be used to predict carcinogenic risk in humans because bis(2-ethylhexyl) phthalate is metabolized differently in rats than in humans. In response, Kluwe et al. (1983) noted that the MTD technically was not exceeded since there were no compound-related effects on survival, the incidence of liver tumors was increased in bis(2-ethylhexyl) phthalate-treated animals regardless of the control data used and the differences in metabolism between rodents and humans would not affect the carcinogenic response in rodents. More recently, Turnbull and Rodricks (1985) concluded that using NTP (1982a) data to estimate bis(2-ethylhexyl) phthalate-induced carcinogenic risk to humans will probably overestimate actual risk. This conclusion was based on the differences between rodents and primates in the metabolism of bis(2-ethylhexyl) phthalate, a nonlinear relationship between the administered dose of bis(2-ethylhexyl) phthalate to the dose of the "proximate carcinogenic species" in rodents, the fact that the "proximate carcinogenic species," which is hypothesized to induce cancer, is produced to a greater extent in

rodents than in primates and that there are differences in target-site sensitivity between humans and rodents for liver tumors in general.

Results of NTP (1982a,b) bioassays indicate that bis(2-ethylhexyl) phthalate is carcinogenic for B6C3F1 mice and F344 rats of both sexes, but are insufficient to assess the carcinogenic potential of butyl benzyl phthalate. The relevance of these studies to the carcinogenic potential of pthalate esters in humans is questionable. Adequate cancer bioassays have not been conducted for other pthalate esters.

4.2.2. Inhalation. Animal bioassays regarding the carcinogenicity of inhaled phthalate esters could not be located in the available literature.

4.3. OTHER RELEVANT DATA

The mutagenicity and genotoxicity of phthalic acid esters have been reviewed by Thomas and Thomas (1984) and Hopkins (1983). Bis(2-ethylhexyl) phthalate and its metabolites have yielded mostly negative results in Ames tests with S. typhimurium, and mixed results with in vitro and in vivo tests of genotoxicity. Diethyl phthalate, dimethyl phthalate and di-n-butyl phthalate were found to be mutagenic in in vitro microbial assays with S. typhimurium (Kozumbo et al., 1982; Rubin et al., 1979; Seed, 1982).

4.4. WEIGHT OF EVIDENCE

In lifetime feeding studies conducted by NTP (1982a), bis(2-ethylhexyl) phthalate was shown to cause increased incidences of liver neoplasms in F344/N rats (hepatocellular carcinoma, hepatocellular carcinoma or neoplastic nodules) and in B6C3F1 mice (hepatocellular carcinoma, hepatocellular carcinoma or adenoma). Based on these results, IARC (1982b) concluded that there is sufficient evidence that bis(2-ethylhexyl) phthalate is carcinogenic for rats and mice. No human studies were available for evaluation.

Using the IARC ranking scheme, bis(2-ethylhexyl) phthalate can be classified as a Group 2B compound. Using the EPA scheme, this compound can be classified as a B2 chemical meaning there is sufficient animal evidence and thus is probably carcinogenic in humans (U.S. EPA, 1986b).

Butyl benzyl phthalate has also been tested for oncogenicity in feeding studies on F344/N rats and B6C3F1 mice (NTP, 1982a,b) (see Table 4-1). Based on the observation of increased incidences of mononuclear cell leukemia and leukemia or lymphoma in female rats, NTP (1982b) concluded that butyl benzyl phthalate was "probably carcinogenic for female F344/N rats." In a separate report, however, Kluwe et al. (1982b) concluded that since the background incidence of myelomonocytic leukemia is normally high in F344/N rats, results presented in NTP (1982b) provide only equivocal evidence of butyl benzyl phthalate-induced cancer in female rats. Furthermore, the fact that dose-related and significant decreases in malignant lymphoma, all lymphoma and leukemia or lymphoma were observed in male mice (NTP, 1982b) adds to the uncertainty that butyl benzyl phthalate may cause cancer in humans. IARC (1982a) concluded that the NTP (1982b) studies are insufficient to assess the carcinogenic potential of butyl benzyl phthalate.

A recent review of the available data by the Carcinogen Assessment Group has concluded that based upon EPA criteria butyl benzyl phthalate is appropriately classified as a Group C, possible human carcinogen.

Other phthalate esters have not been tested for oncogenicity. Therefore, these compounds are best classified as IARC Group 3 and EPA Group D meaning that there is inadequate data to assess the carcinogenic potential.

5. REGULATORY STANDARDS AND CRITERIA

ADIs have been derived for bis(2-ethylhexyl) phthalate, dimethyl phthalate, diethyl phthalate and di-n-butyl phthalate. These are summarized in Table 5-1.

U.S. EPA (1980a) calculated ambient water quality criteria for several of the phthalates, based on contributions from drinking water and consumption of 6.5 g of fish/day. Based on an ADI of 700 mg/day (10 mg/kg/day) from the 2-year rat study by Lehman (1955), a water quality criterion of 313 mg/ℓ was calculated for dimethyl phthalate. For diethyl phthalate, a criterion of 350 mg/ℓ was calculated, based on the ADI of 875 mg/day (13 mg/kg/day) from the rat study by Food Research Labs (1955). A water quality criterion of 34 mg/ℓ for di-n-butyl phthalate was based on the ADI of 8.8 mg/day incorrectly reported as 88 mg/day in U.S. EPA (1980a); the ADI was based on a NOAEL of 125 mg/kg/day from the 52-week study in rats by Smith (1953).

U.S. EPA (1982) derived a human q_1^* for bis(2-ethylhexyl) phthalate of 1.41×10^{-2} $(mg/kg/day)^{-1}$ based on the incidence of hepatocellular adenomas and carcinomas in male mice in the NTP (1980) draft of the chronic cancer study. Water quality criteria of 17.5, 1.75 and 0.175 µg/ℓ were calculated based on consumption of water and fish that may result in estimated increased cancer risk levels of 10^{-5}, 10^{-6} and 10^{-7}, respectively.

TABLE 5-1

ADIs for Phthalate Esters

Ester	ADI (mg/kg/day)	Dose (mg/kg/day)	Species	Reference
bis(2-Ethylhexyl)	0.02	LOAEL = 19	guinea pig	Carpenter et al., 1953
Diethyl	13	NOEL = 1250	rat	Food Research Labs, 1955; U.S. EPA, 1980a
Di-n-butyl	0.1	NOAEL = 125	rat	Smith, 1953; U.S. EPA, 1980a
Dimethyl	10	NOEL = 1000	rat	Lehman, 1955*; U.S. EPA, 1980a

*Incorrectly attributed to Draize et al. (1948) in U.S. EPA (1980a)

6. RISK ASSESSMENT

Risk assessment for phthalate esters should be performed on a compound-by-compound basis, since not all the esters produce the same effects. For example, bis(2-ethylhexyl) phthalate causes testicular atrophy, but when administered in equimolar doses, di-n-octyl phthalate does not (Gray and Butterworth, 1980; Foster et al., 1980); both compounds are 8-carbon diesters.

Quantitative criteria for phthalate esters are summarized in Tables 6-1 through 6-6.

6.1. SUBCHRONIC REFERENCE DOSE (RfD_S)

6.1.1. Oral (RfD_{SO}).

6.1.1.1. BIS(2-ETHYLHEXYL) PHTHALATE -- It is inappropriate to derive an RfD_{SO} for bis(2-ethylhexyl) phthalate because it has been shown to cause liver tumors in F344 rats and B6C3F1 mice (NTP, 1982a).

6.1.1.2. DIETHYL PHTHALATE -- Brown et al. (1978) conducted the only subchronic study on diethyl phthalate that yielded adverse effects. Groups of 15 male and 15 female CD rats were fed diets containing 0, 0.2, 1.0 or 5% diethyl phthalate (0, 150, 770 or 3160 mg/kg/day, males; 0, 150, 750 or 3710 mg/kg/day, females) for 16 weeks. Terminal body weights of male and female rats fed 5% diethyl phthalate were reduced significantly in comparison with controls. Although slight but significant changes were seen in females at the 1% level, the use of multiple T tests for the comparisons (without correction) and the small magnitude of the changes suggests that the 1% feeding level (750 mg/kg/day) represents a NOAEL in this study and could be used in the derivation of an RfD_{SO}. In a 2-year study on rats (Food Research Labs, 1955) significant reduction in body weight was observed in

49900

TABLE 6-1

Summary Table for Bis(2-ethylhexyl) Phthalate

Route	Species	Experimental Exposure/Dose	Effect	q_1^* or Unit Risk	Reference
Oral	mouse (male)	0, 3000 or 6000 ppm diet for 103 weeks (0, 672, 1325 mg/kg/day)	liver tumors	8.36×10^{-3} $(mg/kg/day)^{-1}$	NTP, 1982a
Inhalation	ND	ND	ND	ND	ND

ND = No data

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TABLE 6-2

Summary Table for Diethyl Phthalate*

Oral	Species	Experimental Exposure/Dose	Effect	RfD or CS	Reference
RfD_{SO}	rat	1% diet for 16 weeks (750 mg/kg/day)	slight body weight reduction in females	525 mg/day	Brown et al., 1978
RfD_{O}	rat	1% diet for 16 weeks (750 mg/kg/day)	slight body weight reduction in females	52.5 mg/day	Brown et al., 1978
Maximum CS	mouse	2.5% diet for two generations (3250 mg/kg/day) (RV_d=1)	reduced reproductive capacity (RV_e=8)	8	Reel et al., 1984

*Only oral data were available.

TABLE 6-3

Summary Table for Di-n-butyl Phthalate*

Oral	Species	Experimental Exposure/Dose	Effect	RfD or CS	Reference
RfD_{SO}	rat	0.25% diet for 52 weeks (125 mg/kg/day)	none	88 mg/day	Smith, 1953
RfD_O	rat	0.25% diet for 52 weeks (125 mg/kg/day)	none	8.8 mg/day	Smith, 1953; U.S. EPA, 1980a
Maximum CS	mouse	80 mg/kg/day during days 0-18 of gestation (2100 mg/kg/day) (RV_d=1.6)	fetotoxicity, teratogenicity, maternal toxicity (RV_e=8)	12.8	Shiota and Nishimura, 1982; Shiota et al., 1980

*Only oral data were available.

TABLE 6-4

Summary Table for Dimethyl Phthalate*

Oral	Species	Experimental Exposure/Dose	Effect	RfD or CS	Reference
RfD_{SO}	rat	2% diet for 2 years (1000 mg/kg/day)	none	ND	NA
RfD_O	rat	2% diet for 2 years (1000 mg/kg/day)	none	ND	NA
Maximum CS	rat	8% diet for 2 years (1000 mg/kg/day) (RV_d=1)	chronic nephritis (RV_e=7)	7	Lehman, 1955

*Only oral data were available.

ND = Not determined; NA = not applicable

TABLE 6-5

Summary Table for Butyl Benzyl Phthalate[a]

Oral	Species	Experimental Exposure/Dose	Effect	RfD or CS	Reference
RfD_{SO}	rat	0.28% diet for 26 weeks (159 mg/kg/day)	none	111 mg/day	NTP, 1985
RfD_O	rat	0.28% diet for 26 weeks (159 mg/kg/day)	none	11.1 mg/day	NTP, 1985
Maximum CS	rat (male)	6000 ppm for 28 weeks (300 mg/kg/day) (RV_d=1.7)[b]	early, high mortality (RV_e=10)	17	NTP, 1982b

[a]Only oral data were available.

[b]An uncertainty factor of 10 was applied because excessive mortality occurred as early as 15 weeks in the study

TABLE 6-6

Summary Table for Di-n-octyl Phthalate[a,b]

Oral	Species	Experimental Exposure/Dose	Effect	RfD or CS
RfD_{SO}	rat	3500 ppm diet for 7-12 months (175 mg/kg/day)	Increased SGPT and SGOT; increased liver and kidney weights	ND
RfD_O	rat	3500 ppm diet for 7-12 months (175 mg/kg/day)	Increased SGPT and SGOT; increased liver and kidney weights	ND
Maximum CS	rat	3500 ppm diet for 7-12 months (175 mg/kg/day) (RV_d=1)	Increased SGPT and SGOT; increased liver and kidney weights(RV_e=6)	6

[a]Source: Piekacz, 1971

[b]Only oral data were available.

ND = Not determined

rats fed 5% diethyl phthalate but not in rats fed ≤2.5%. Deficiencies in the reporting of the Food Research Study, however, reduce confidence in the use of these data. Therefore, the NOAEL of 750 mg/kg/day is chosen as the basis for the RfD_{SO}. Applying an uncertainty factor of 10 for interspecies extrapolation and 10 for interindividual variability results in an RfD_{SO} of 8 mg/kg/day or 525 mg/day.

6.1.1.3. DI-n-BUTYL PHTHALATE -- U.S. EPA (1980a) derived an ADI of 0.1 mg/kg/day based on a 52-week oral rat NOAEL of 125 mg/kg/day (Smith, 1953) and an uncertainty factor of 1000. A higher dose (1.25% in the diet or 625 mg/kg/day) caused 50% mortality within 1 week of the initial exposure (Smith, 1953).

Onda et al. (1974) observed the formation of renal cysts in the F_1 and F_2 generations of mice exposed orally to either 10 or 100 mg/kg/day for 3 generations. These doses are below the NOAEL used by U.S. EPA (1980a) to derive the ADI for di-n-butyl phthalate. Since no details of the Onda et al. (1974) study were reported, it was not considered in risk assessment.

When 0.12 or 0.6 mg/kg/day (120 or 600 mg/kg) di-n-butyl phthalate was administered to rats by gavage during gestation, an increased number of resorptions and reduced fetal body weight were observed at the 600 mg/kg dose (Nikonorow et al., 1973). No gross skeletal effects were observed. Maternal toxicity was not reported, but significantly reduced placental weights were observed at both doses. Since there were no effects on reproductive or fetal endpoints in rats exposed to 120 mg/kg/day, the reduced placental weight probably represents a NOAEL. The LOAEL for this study (600 mg/kg/day) is well above the NOAEL (125 mg/kg/day) used to derive the ADI.

Shiota et al. (1980) and Shiota and Nishimura (1982) observed maternal toxicity, fetotoxicity and gross external malformations in mice fed 1% di-n-butyl phthalate in the diet (2100 mg/kg/day, as provided by the investigators) on days 0-18 of gestation. Significantly reduced numbers of ossified coccygia were observed at all levels of treatment (80, 180, 370 or 660 mg/kg/day), but there were no significant differences between controls and treated mice in incidences of skeletal malformations, lumbar rib variations or delayed sternal ossification. Doses $\leq$660 mg/kg/day would therefore represent NOAELs for this study and 2100 mg/kg/day represents a FEL. Di-n-butyl phthalate has been shown to cause testicular atrophy in rats, but only at doses greater than the NOAEL (123 mg/kg/day) used to derive the ADI (Cater et al., 1976, 1977; Gray et al., 1982; Gray and Butterworth, 1980). The RfD_{SO} for di-n-butyl phthalate can therefore be based on the rat NOAEL of 123 mg/kg/day defined by Smith (1953). Dividing 125 mg/kg/day by an uncertainty factor of 100 (10 for differences in sensitivity among humans; 10 for interspecies extrapolation) yields an RfD_{SO} of 1.25 mg/kg/day or 88 mg/day for a 70 kg human.

6.1.1.4. **DIMETHYL PHTHALATE** -- Studies pertaining to the subchronic toxicity of dimethyl phthalate could not be located in the available literature.

6.1.1.5. **BUTYL BENZYL PHTHALATE** -- Butyl benzyl phthalate has been tested for oncogenicity in feeding studies on F344 rats and B6C3F1 mice (NTP, 1982b). Statistically significant increases in the incidences of mononuclear cell leukemia and leukemia or lymphoma were observed in female rats. However, because of the naturally high background incidence of myelomonocytic leukemia in F344 rats, and because dose-related and significant decreases in malignant lymphoma, all lymphoma and leukemia or lymphoma were

observed in male mice in the same study, there is limited evidence to conclude that butyl benzyl phthalate is carcinogenic. IARC (1982a) concluded that the NTP (1982b) studies are insufficient to assess the carcinogenic potential of butyl benzyl phthalate. It is not appropriate to derive a q_1^* for butyl benzyl phthalate until further testing is performed. Butyl benzyl phthalate has been classified as a Group C, possible human carcinogen, using the EPA weight-of-evidence criteria.

Increased mortality that was due to unexplained hemorrhaging was observed in male F344 rats fed 6000 or 12,000 ppm butyl benzyl phthalate (300 or 600 mg/kg/day, using a food factor of 0.05) (NTP, 1982b). The study was terminated after 28 weeks. In 90-day feeding studies on rats conducted by Monsanto (1972), rats were fed 0, 0.25, 0.5, 1.0, 1.5 or 2% (0, 125, 250, 500, 750 or 1000 mg/kg/day) butyl benzyl phthalate and dogs were fed 0, 1, 2 or 5% (0, 250, 500 or 1250 mg/kg/day) butyl benzyl phthalate. No adverse effects were observed among dogs fed butyl benzyl phthalate at any level, or among rats fed 125 or 250 mg/kg/day butyl benzyl phthalate. Dietary concentrations of 2.5 or 5% have been shown to cause testicular atrophy in a 14-day study on rats (Agarwal et al., 1985).

In the NTP (1985) study, rats were fed dietary levels of 0, 0.03, 0.09, 0.28, 0.83% and 2.5% butyl benzyl phthalate. Using data presented in the report, these dietary levels correspond to ~0, 17, 51, 159, 470 and 2875 mg/kg/day. At 2.5%, weight gain was significantly depressed and testicular and kidney lesions were apparent. In addition, liver-to-body weight ratios were increased and hematological evaluations suggested a pattern of increased erythrocyte turnover. At 0.83%, the only effects noted were increased absolute liver weight, increased liver-to-body weight and liver-to-brain weight ratios and increases in mean corpuscular hemoglobin.

Using the NOEL (0.28%) of 159 mg/kg/day and applying an uncertainty factor of 100, an RfD_{SO} of 111 mg/day could be developed; however, this value would not be protective for potential carcinogenic effects of this compound.

6.1.1.6. **DI-n-OCTYL PHTHALATE** -- The only available toxicity study on di-n-octyl phthalate was reported in an abstract by Piekacz (1971), in which Wistar rats were given either 0 or 3500 ppm di-n-octyl phthalate in the diet for 7-12 months. Assuming that a rat consumes the equivalent of 5% of its weight in food/day, 3500 ppm corresponds to a dose of 175 mg/kg/day. Females had elevated kidney and liver weights, and both males and females had increased SGOT and SGPT. In rats, di-n-octyl phthalate did not cause testicular atrophy when given orally at a dose equimolar to that at which bis(2-ethylhexyl) phthalate caused testicular atrophy (Gray and Butterworth, 1980; Foster et al., 1980). Furthermore, adverse effects on reproduction and fertility were not observed in 2 generations of CD-1 mice fed 1.25, 2.5 or 5% (12,500-50,000 ppm) di-n-octyl phthalate in the diet (Gulati et al., 1985). Inadequate data are presented in the abstract to support RfD_{SO} estimation.

6.1.2. **Inhalation (RfD_{SI}).** Subchronic or chronic inhalation studies on phthalate esters could not be located in the available literature. Therefore, it is not possible to derive RfD_{SI} values.

6.2. **REFERENCE DOSE (RfD)**

6.2.1. **Oral (RfD_O).**

6.2.1.1. **BIS(2-ETHYLHEXYL) PHTHALATE** -- Since bis(2-ethylhexyl) phthalate was found to cause liver tumors in F344 rats and B6C3F1 mice (NTP, 1982a), it is inappropriate to derive an RfD_O or a CS for chronic toxicity.

6.2.1.2. DIETHYL PHTHALATE -- Only two chronic studies were available for use in the derivation of an RfD_0 and a CS for diethyl phthalate.

U.S. EPA (1980a) derived an ADI of 13 mg/kg/day for diethyl phthalate based on a chronic oral rat NOEL of 1250 mg/kg/day (2.5% diet) (Food Research Labs, 1955) and an uncertainty factor of 100. Higher doses (5% diet) caused a reduction in body weight. A 2-generation reproduction study by Reel et al. (1984) demonstrated that F_1 but not parental mice exposed to 2.5% diethyl phthalate in the diet had fewer pups/litter, increased liver weights (males and females), increased prostate weights, decreased sperm concentration and increased pituitary weight (females only) in comparison with controls. Assuming that mice consume food equivalent to 13% of their body weight/day, 2.5% is equivalent to 3250 mg/kg/day, a value well above the NOEL (1250 mg/kg/day) used to derive the ADI. Diethyl phthalate did not cause testicular atrophy in rats (Gray and Butterworth, 1980; Foster et al., 1980).

Although in general it is preferable to utilize chronic data over subchronic data for RfD development, deficiencies in reporting of the Food Research study reduce confidence in the data. Therefore, the subchronic study of Brown et al. (1978) is chosen as the basis of the RfD_0. This study defined a NOAEL of 750 mg/kg/day with decreased body weight and increased liver weight seen at the next highest exposure level. Applying an uncertainty factor of 1000 (10 for subchronic to chronic, 10 for interspecies variability and 10 for interindividual variability) results in an RfD_0 of 0.75 mg/kg/day, or 52.5 mg/day for a 70 kg human.

The highest CS can be derived from the study of Reel et al. (1984) on the basis of the adverse reproductive effects observed among mice exposed to 2.5% diethyl phthalate in the diet. Assuming that a mouse consumes food

equivalent to 13% of its body weight/day, 2.5% is equivalent to a dose of 3250 mg/kg/day. Multiplying 3250 mg/kg/day by the cube root of the ratio of the reference mouse weight (0.03 kg) to reference human weight (70 kg), and by the human weight (70 kg) yields a human MED of 17,152 mg/day, which corresponds to an RV_d of 1. An RV_e of 8 is assigned on the basis of reduced reproductive capacity. Multiplying the RV_e by the RV_d yields a CS of 8. U.S. EPA (1983b) derived an RQ of 5000 based on the 2-year study by Food Research Labs (1955), in which rats had significantly reduced body weight gain (RV_e=4) at a dietary level of 5% (2500 mg/kg/day; MED=29,925; RV_d=1). The resulting CS is 4. The reproduction study by Reel et al. (1984) was not available during the preparation of the previous RQ document (U.S. EPA, 1983b).

6.2.1.3. **DI-n-BUTYL PHTHALATE** -- No effects were observed in chronic studies on the toxicity of di-n-butyl phthalate in rats (LeFaux, 1968). Because these chronic studies failed to define a threshold for toxicity, an RfD_0 for di-n-butyl phthalate can be based on the subchronic study by Smith (1953) using rats. A higher dose (1.25% diet or 625 mg/kg/day) caused 50% mortality within 1 week of administration (Smith, 1953). An RfD of 0.12 mg/kg/day can be derived by dividing the NOAEL of 125 mg/kg/day by an uncertainty factor of 1000 (10 for interspecies extrapolation; 10 for using a subchronic study to estimate chronic toxicity; 10 for differences in sensitivity among humans). This RfD, equivalent to 8.6 mg/day for a 70 kg human, is adopted as the RfD_0 for di-n-butyl phthalate. However, it is noted that the study has a number of deficiencies.

There are a number of studies from which CSs for di-n-butyl phthalate can be derived. The most severe effects were the fetotoxicity, teratogenicity and maternal toxicity in mice exposed orally to 2100 mg

di-n-butyl phthalate/kg/day (Shiota and Nishimura, 1982; Shiota et al., 1980). These effects warrant an RV_e of 9. Multiplying 2100 mg/kg/day by the product of the cube root of the ratio of mouse weight (0.03 kg; measured) to reference human weight (70 kg), and by the human weight (70 kg) yields a human MED of 11,083 mg/day, which corresponds to an RV_d of 1. Multiplying the RV_e by the RV_d yields a CS of 9.

Shiota et al. (1980) and Shiota and Nishimura (1982) also observed significantly reduced numbers of ossified coccyges at all levels of treatment (80, 180, 370, 660 or 2100 mg/kg/day), but there were no significant differences between controls and treated mice in incidences of skeletal malformations, lumbar rib variations or delayed sternal ossification. In a previous RQ determination, U.S. EPA (1983a) used delayed ossification at 80 mg/kg/day as the basis for the RQ of 1000. The corresponding MED for this dose level is 420 mg/day; the RV_d is 1.6. An RV_e of 8 is appropriate for fetotoxicity resulting in a CS of 12.8.

6.2.1.4. DIMETHYL PHTHALATE -- U.S. EPA (1980a) derived an ADI of 10 mg/kg/day for dimethyl phthalate based on a chronic rat NOEL of 1000 mg/kg/day and an uncertainty factor of 100. Higher doses caused chronic nephritis and decreased growth rate (Lehman, 1955). There are no other chronic oral studies for dimethyl phthalate. No adverse effects upon reproduction, growth or survival of offspring were observed in mice gavaged with dimethyl phthalate (3500 mg/kg) on days 7-15 of gestation (Booth et al., 1983; Plasterer et al., 1985). The pups were not examined for malformations. Furthermore, testicular effects were not observed in rats gavaged with dimethyl phthalate at doses equimolar to those at which bis(2-ethylhexyl) phthalate caused testicular atrophy in rats (Gray and Butterworth, 1980; Foster et al., 1980). A reevaluation of the Lehman (1955) study suggests

that the data, as presented in this paper, is inadequate for development of an RfD_0.

Lehman (1955) observed chronic nephritis (RV_e=7) in rats fed 8% dimethyl phthalate and decreased body weight (RV_e=4) in rats fed 4% dimethyl phthalate for 2 years. Assuming that a rat consumes 5% of its weight in food per day, 8% is equivalent to a dose of 4000 mg/kg/day and 4% is equivalent to 2000 mg/kg/day. Multiplying 2000 and 4000 mg/kg/day by the product of the cube root of the ratio of rat weight (0.35 kg; assumed) to human weight (70 kg; assumed), and by human weight (70 kg) yields human MEDs of 23,940 and 47,879 mg/day, respectively. Both MEDs correspond to RV_ds of 1. Multiplying the RV_d by the RV_es of 4 and 7 yields CSs of 4 and 7, respectively.

6.2.1.5. **BUTYL BENZYL PHTHALATE** -- The only chronic studies on butyl benzyl phthalate are the oncogenicity studies by NTP (1982b) on F344 rats and B6C3F1 mice. Female rats received 0, 6000 or 12,000 ppm and mice of both sexes received 0, 3000 or 6000 ppm for 103 weeks. Male rats also received 0, 6000 or 12,000 ppm but the study was terminated after 28 weeks because of high, dose-related mortality among treated rats. Mortality was attributed to unexplained hemorrhaging. The only other noncarcinogenic effect was reduction in growth rate among all treated mice and treated female rats, although the reduction in growth among female rats was accompanied by reduced food consumption. Data on food consumption were not reported for mice. Since these data do not provide a clear NOAEL or LOAEL, this experiment is not suitable for risk assessment and it is best to derive the RfD_0 from the subchronic data used to derive the RfD_{SO}. An RfD_0 of 11.1 mg/day could be proposed based upon the NOEL of 159 mg/kg/day (0.28%) from the NTP (1985) study by applying an additional uncertainty factor of 10 to the RfD_{SO}, which is described in Section 6.1.1.5.

However, this estimate would not be protective for potential carcinogenic effects of butyl benzyl phthalate.

The highest CS for butyl benzyl phthalate is based on early dose-related mortality among male F344 rats fed 6000 or 12,000 ppm for 28 weeks (NTP, 1982b). In the subchronic study by Monsanto (1972), the only effect in rats treated for 90 days was increased liver weight at concentrations $\geq$10,000 ppm; the only effect in dogs was decreased initial growth at 50,000 ppm because of their refusal to eat. There were no other studies available that could be considered in the derivation of a CS for butyl benzyl phthalate.

Since there is no explanation why compound-related early mortality was observed among male rats in the NTP (1982b) study but not in the Monsanto (1972) study, a CS is derived on the basis of mortality among male rats fed 6000 ppm for 28 days. Assuming that a rat consumes food equivalent to 5% of its body weight/day, 6000 ppm is equivalent to 300 mg/kg/day. Multiplying 300 mg/kg/day by the cube root of the ratio of rat weight (0.375 kg in the study) to human weight (70 kg) and by the human weight (70 kg) yields an equivalent human dose of 3674 mg/day. Because the mortality occurred during 15-28 weeks, the dose should be divided by an uncertainty factor of 10. The resultant MED of 367 mg/day corresponds to an RV_d of 1.7. Multiplying the RV_d by the RV_e of 10 for mortality results in a CS of 17.

6.2.1.6. **DI-n-OCTYL PHTHALATE** -- Chronic studies on the toxicity of di-n-octyl phthalate could not be located in the available literature. One abstract of a subchronic study (described in Section 6.1.1.6.) was located. However, inadequate data were presented to allow RfD_0 development.

A CS of 6 can be derived from Piekacz (1971) on the basis of elevated liver and kidney weights (female rats) and increased SGOT and SGPT (male and female) in rats fed 3500 ppm di-n-octyl phthalate. Assuming that a rat con-

sumes food equivalent to 5% of its body weight/day, 3500 ppm is equivalent to a dose of 175 mg/kg/day. Multiplying 175 mg/kg/day by the cube root of the ratio of rat weight (0.35 kg; assumed) to human weight (70 kg; assumed) and human weight yields a human MED of 2095 mg/day. The MED is assigned an RV_d of 1. The RV_e of 6 is assigned on the basis of the above effects. Multiplying the RV_d by the RV_e yields a CS of 6.

6.2.2. Inhalation. Data pertaining to the toxicity of inhaled phthalate esters could not be located in the available literature.

6.3. CARCINOGENIC POTENCY (q_1^*)

6.3.1. Oral. Evidence of oncogenic potential sufficient for computation of carcinogenic potency has been generated only for bis(2-ethylhexyl) phthalate (NTP, 1982a).

Using data from NTP (1982a), q_1^*s can be derived for combined hepatocellular carcinoma and neoplastic nodules in rats, and combined hepatocellular carcinoma and adenoma in mice using the computerized multistage model developed by Howe and Crump (1982). The highest value, an adjusted human interim q_1^* of 8.36×10^{-3} $(mg/kg/day)^{-1}$ was obtained from data on male mice (Table 6-7). Turnbull and Rodricks (1985) have cautioned that using rodent data to estimate bis(2-ethylhexyl) phthalate-promoted carcinogenic risk to humans may overestimate the actual risk. This caution was based on several factors including differences between rodents and primates in the metabolism of bis(2-ethylhexyl) phthalate, a nonlinear relationship between the administered dose of bis(2-ethylhexyl) phthalate and the dose of the hypothesized "proximate carcinogenic species" in rodents, the fact that the hypothesized proximate carcinogenic species is produced to a greater extent in rodents than in primates, and differences in target site sensitivities between humans and rodents for liver tumors in general. These factors have not yet been evaluated by the EPA. As a result, the proposed interim q_1^*

TABLE 6-7

Cancer Data Sheet for Derivation of q_1^*

Compound: bis(2-ethylhexyl) phthalate

Reference: NTP, 1982a

Species, strain/sex: mouse, B6C3F1, male

Body weight: 0.04 kg (measured)

Length of exposure (le) = 103 weeks

Length of experiment (Le) = 105 weeks (0, low dose); 104 weeks (high dose)

Lifespan of animal (L) = 105 weeks (0, low dose); 104 weeks (high dose)

Tumor site and type: hepatocellular carcinoma or adenoma

Route/vehicle: oral, diet

Experimental Doses or Exposures[a] (mg/kg/day)	Transformed Dose[b] (mg/kg/day)	Incidence No. Responding/No. Examined
0	0	14/50
672	54.70	25/48
1325	108.89	29/50

[a]The mice were given 3000 or 6000 ppm in the diet; the doses in mg/kg/day were provided by NTP (1982b).

[b]Dose x le/Le x $(WA/70)^{1/3}$ x $(Le/L)^3$ = transformed dose where L=Le; WA = mouse body weight

Unadjusted q_1^* from study = not calculated (see text)

Human $q_1^* = 8.36 \times 10^{-3}$ $(mg/kg/day)^{-1}$

value may be revised at a later date. Di(2-ethylhexyl)phthalate is a Group B2 carcinogen using the U.S. EPA weight-of-evidence approach, meaning that there are sufficient animal data and the compound is considered a probable human carcinogen.

NTP (1982b) conducted cancer bioassays of butyl benzl phthalate in both F344/N rats and B6C3F1 mice. No treatment related increases in incidence of either neoplastic or non-neoplastic lesions were noted in either sex of mice.

In rats, increased mortality due to "unexplained internal hemorrhage" was observed in treated males beginning at the 14th treatment week. This portion of the study was terminated after 28 weeks. Female rats showed increased incidence of mononuclear cell leukemia and leukemia or lymphoma at the high dose (1200 ppm). Since the background incidence of leukemia is normally high in F344/N rats, and because decreases in incidence of malignant lymphoma, all lymphoma or leukemia were seen in male mice this was considered to be equivocal evidence of carcinogenicity. Butyl benzyl phthalate is considered a Group C, possible human carcinogen using the U.S. EPA weight-of-evidence classification system. Data were considered inadequate for quantitative risk assessment.

6.3.2. Inhalation. The oncogenicity of inhaled phthalate esters has not been tested.

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